1350971

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C2P 1L1 1L2 2E12B 2E13 2E14 2E18B 2E18C 2E19C 2E19D 2E19E 2E26A 2E26B 2E26D 3B12B 3B13 3B14A 3B18B 3B18C 3B18D 3B19C 3B19D 3B19E 3C12B 3C13 3C14 3C18B 3C18C 3C19C 3C19F 3C30A 3C30B 7 8

C3S 1C 1D 3A 3D 5 6 7B 7D 9

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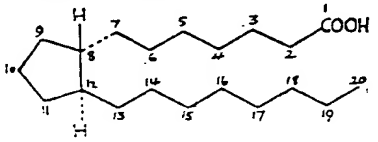
(54) CYCLOPENTANE DERIVATIVES

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, Imperial Chemical House, Millbank, London, SW1P 3JF, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

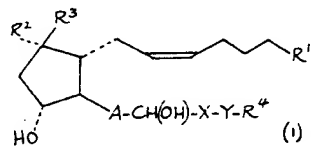
This invention relates to new cyclopentane derivatives, and in particular it relates to new cyclopentane derivatives which are analogues of the naturally occurring compounds known as prostaglandin $F_{2\alpha}$ and prostaglandin E_2, showing a similar spectrum of pharmacological properties and being useful for similar purposes. The relative potency of the new compounds, however, in respect of the particular pharmacological effects shown is different from that of the above naturally occurring prostaglandins, and in particular they are more potent as luteolytic agents than the corresponding natural prostaglandins. That is to say, the prostaglandin $F_{2\alpha}$ analogues of the present invention are more potent than natural prostaglandin $F_{2\alpha}$, and the prostaglandin E_2 analogues of the present invention are more potent than natural prostaglandin E_2. The new compounds are, in a similar way, more potent as stimulants of uterine smooth muscle than the corresponding natural prostaglandins $F_{2\alpha}$ and E_2, and the prostaglandin E_2 analogues of the invention are particularly valuable in this respect. The new compounds are therefore advantageous when used as contraceptives, for the termination of pregnancy or for control of the oestrus cycle, as hypotensives or for the relief of bronchospasm. The new compounds of the invention are also useful for addition to semen intended for artificial insemination of domestic animals, the success rate of insemination being thereby increased, especially in pigs.

The cyclopentane derivatives described in this specification will be named as derivatives of prostanoic acid of the formula shown below and numbered as shown: —



[Price 25p]

According to the invention there is provided a prostanoic acid derivative of the formula: —



(I)

wherein R^1 is a hydroxymethyl or carboxy radical, or an alkoxycarbonyl radical of up to 11 carbon atoms; either R^2 is a hydroxy radical or an alkanoyloxy radical of 1 to 4 carbon atoms and R^3 is a hydrogen atom, or R^2 and R^3 together form the oxo radical; A is an ethylene or transvinylene radical; X is an alkylene radical of 1 to 3 carbon atoms bearing as substituents 0, 1 or 2 alkyl radicals, each of 1 to 3 carbon atoms; Y is an oxygen or sulphur atom, a sulphinyl (—SO—) radical or an alkylimino (-NAlkyl-) radical of up to 4 carbon atoms; and R^4 is an aryl, benzyl or furfuryl radical which is unsubstituted or which is substituted by hydroxy or halogen atoms, nitro or phenyl radicals, alkyl, alkenyl, halogenoalkyl, alkoxy, alkenyloxy or acylamino radicals of up to 4 carbon atoms or dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms; which compound contains 0 or 1 alkyl radicals of up to 4 carbon atoms on carbon atoms 2, 3 or 4; and for those compounds wherein R^1 is a carboxy radical, the pharmaceutically acceptable salts thereof.

A suitable value for R^1 when it is an alkoxycarbonyl radical of up to 11 carbon atoms is, for example, the methoxycarbonyl ethoxycarbonyl, n butoxycarbonyl or n-decyloxycarbonyl radical, preferably an alkoxycarbonyl radical of up to 6 or 7 carbon atoms.

A suitable value for R^2 when it is an alkanoyloxy radical of 1 to 4 carbon atoms is, for example, the acetoxy or propionyloxy

A suitable value for X when it is an alkylene radical of 1 to 3 carbon atoms bearing as substituents 0, 1 or 2 alkyl radicals, each of 1 to 3 carbon atoms is, for example a methylene, ethylene or trimethylene radical bearing 0, 1 or 2 methyl substituents, for example the methylene, ethylidene, isopropylidene and trimethylene radicals.

A suitable value for Y when it is an alkylimino radical of up to 4 carbon atoms is, for example, the methylimino (CH_3—N<) radical.

A suitable value for A is the *trans*-vinylene radical.

A suitable value for R^4 when it is an aryl radical optionally substituted, is for example a phenyl, naphthyl, or furfuryl benzyl radical optionally substituted by not than two halogen atoms, phenyl, hydroxy, methyl, t-butyl, allyl, methoxy, or allyloxy radicals, chloroallyl or fluoroalkyl each of 1 to 4 carbon atoms or dimethylamino radicals.

Suitable halogen atom substituents in R^4 are, for example, chlorine, bromine or fluorine atoms. Suitable alkyl, alkoxy, alkenyl or alkenyloxy substituents of up to 4 carbon atoms in R^4 are, for example methyl, t-butyl, allyl, methoxy or allyloxy radicals. Suitable halogenoalkyl substituents of 1 to 4 carbon atoms in R^4 are, for example chloroalkyl or fluoroalkyl radicals, for example trifluoromethyl radicals. Suitable dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms, which may be substituents in R^4 are, for example, dialkylamino radicals wherein the two alkyl radicals are the same, for example the dimethylamino radical.

Suitable substituted aryl radicals are for example, chlorophenyl, chloronaphthyl, bromophenyl, fluorophenyl, tolyl, xylyl, methylnaphthyl, t-butylphenyl, methylchlorophenyl, trifluoromethylphenyl, hydroxyphenyl, methoxyphenyl, methoxynaphthyl, biphenylyl, dimethylaminophenyl and tetrahydronaphthyl radicals.

Preferred aryl radicals contain not more than two substituents as defined above. Particular values for R^4 are, therefore, the phenyl, benzyl, furfuryl, 1-naphthyl, 2-naphthyl, 2-, 3- and 4-chlorophenyl, 4-bromophenyl, 2-, 3- and 4- fluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dichlorophenyl, 2-, 3- and 4-tolyl, 2,3-, 3,4- and 3,5-xylyl, 4-t-butylphenyl, 3-allylphenyl, 3-trifluoromethylphenyl, 4-hydroxyphenyl, 2-, 3- and 4-methoxyphenyl, 4-biphenylyl, 3-dimethylaminophenyl, 2-chloro-4-methylphenyl, 1-chloro-2-naphthyl, 4-chloro-2-naphthyl, 6-methyl-2-naphthyl, 6-methoxy-2-naphthyl and 5,6,7,8-tetrahydro-2-naphthyl radicals.

A suitable value for the alkyl radical of up to 4 carbon atoms which may be present as a substituent on carbon atom 2, 3 or 4 is, for example the methyl radical.

Examples of base-addition salts are the ammonium, alkyl-ammonium containing 1 to 4 alkyl radicals each of 1 to 6 carbon atoms, alkanolammonium containing 1 to 3 2-hydroxyethyl radicals, and alkali metal salts, for example the triethylammonium, ethanolammonium, diethanolammonium, sodium and potassium salts.

It will be observed that the compounds of the formula I contain at least five asymmetric carbon atoms, namely carbon atoms 8, 9, 11, 12 and 15, the configurations at four of which, 8, 9, 11 and 12 are specified in formula I, and that carbon atoms 2, 3 and 4 may also be asymmetrically substituted, so that it is clear that such compounds can exist in at least two optically active forms. It is to be understood that the useful properties of the racemate may be present to differing extents in the optical isomers, and that this invention relates

to the racemic form of the compounds of formula I and any optically active form which shows the above useful properties, it being a matter of common general knowledge how the optically active forms may be obtained, and to determine their respective biological properties.

It is also to be understood that the above definition encompasses both C-15 epimers and that in all chemical formulae shown hereafter in this specification, the same fixed stereo-chemistry at C-8, 9, 11 and 12 as that shown in formula I is implied.

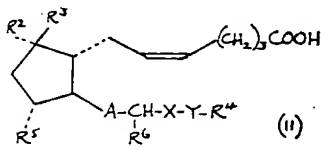
Although both C-15 epimers of a compound of the invention possess desirable pharmacological properties, that epimer which is more polar on thin layer chromatography is the more active, for example in the luteolytic test, and the more polar C-15 epimers are therefore preferred.

A preferred group of cyclopentane derivatives of the invention, because of their high luteolytic or smooth muscle stimulant properties, comprises those compounds wherein R^4 is a chlorophenyl, fluorophenyl, trifluoromethylphenyl or unsubstituted naphthyl radical, especially those compounds wherein R^1 is the carboxy, methoxycarbonyl or hydroxymethyl radical, and particularly those compounds wherein R^4 is the 3- or 4-chlorophenyl, 2- or 4-fluorophenyl, 3-trifluoromethylphenyl or unsubstituted naphthyl radical. A particularly preferred sub-group comprises those compounds wherein R^1 is the carboxy, methoxycarbonyl or hydroxymethyl radical, R^2 is the hydroxy radical and R^3 is a hydrogen atom, or R^2 and R^3 together form the oxo radical, A is the *trans*-vinylene radical, X is the methylene or isopropylidene radical, Y is an oxygen atom and R^4 is the 3- or 4-chlorophenyl, 2- or 4-fluorophenyl, 3-trifluoromethylphenyl or 2-naphthyl radical, optionally bearing a methyl substituent on carbon atom 2.

Particular preferred compounds of the invention are 16 - (4 - fluorophenoxy) - 9α,11α,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid, methyl 16 - (4 - fluorophenoxy) - 9α,11α,15-trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoate, 16 - (2 - fluorophenoxy) - 9α,11α,15 - trihydroxy-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoic acid, 16 - (4 - chlorophenoxy)-9α,11α,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid, methyl 16 - (4 - chlorophenoxy) - 9α,11α,15-trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoate, 16 - (4 - chlorophenoxy) - 9α,11α,15 - trihydroxy-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienol, 16 - (3 - chlorophenoxy)-9α,11α,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid, methyl 16 - (3 - chlorophenoxy) - 9α,11α,15-trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoate, 16 - (3 - chlorophenoxy) - 9α,11α,15 - trihydroxy - 2 - methyl-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienol, 9α,11α,15 - trihydroxy - 16-(3 - trifluoromethylphenoxy) - 17,18,19,20-tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid, 9α,11α,15 - trihydroxy - 16 - (2-naphthyloxy) - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoic acid, 16 - (4-chlorophenoxy) - 9α,11α,15 - trihydroxy-16,16 - dimethyl - 17,18,19,20 - tetranor-5 - *cis* - 13 - *trans* - prostadienoic acid and 16 - (4 - chlorophenoxy) - 11α,15 - dihydroxy-9 - oxo - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoic acid.

The cyclopentane derivatives of the invention may be manufactured by methods known in themselves for the manufacture of chemically analogous compounds. Thus, the following processes for the manufacture of the cyclopentane derivative of the formula I, are provided as further features of the invention:—

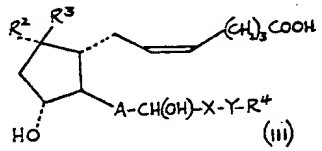
(a) for those compounds wherein R^1 is a carboxy radical, the hydrolysis of a compound of the formula:—



(II)

or of a mixed anhydride thereof, wherein A, X, Y, R^2, R^3 and R^4 have the meanings stated above, and R^5 and R^6 are each a tetrahydropyran - 2 - yloxy radical, or an acyloxy radical of 1 to 6 carbon atoms, whereafter when a salt is required the product is reacted with a base; or

(b) for those compounds wherein R^1 is an alkoxycarbonyl radical of up to 11 carbon atoms, the reaction of an acid of the formula:—



(III)

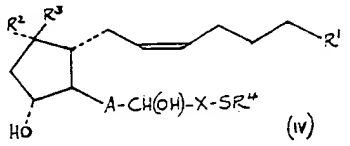
wherein A, X, Y, R^2, R^3 and R^4 have the meanings stated above, with a diazoalkane of the formula $R^7.N_2$, wherein R^7 is an alkyl radical of 1 to 10 carbon atoms; or

(c) for those compounds wherein R^1 is an alkoxycarbonyl radical of up to 11 carbon atoms, the reaction of a salt, for example the silver salt, of an acid of the formula III, with an alkyl halide of 1 to 10 carbon atoms, for example the alkyl iodide; or

(d) for those compounds wherein R^1 is the

hydroxymethyl radical and Y is the oxygen or sulphur atom, or an alkylimino radical, the reduction of an ester of the formula I wherein R^1 is an alkoxycarbonyl radical, for example an alkoxycarbonyl radical of up to 11 carbon atoms, for example with a complex metal hydride, for example lithium aluminium hydride, or

(e) for those compounds wherein Y is the sulphinyl radical, the oxidation of a thio-compound of the formula:—



(IV)

wherein R^1, R^2, R^3, R^4, A and X have the meanings defined in claim 1, for example with sodium periodate.

A suitable mixed anhydride is a mixed anhydride with a lower alkanoic acid, for example a lower alkanoic acid of up to 8 carbon atoms, for example acetic acid.

The hydrolysis in process (a) may be carried out under either acidic or basic conditions, for example in aqueous acetic acid, or in an aqueous or alcoholic solution of an alkali metal carbonate, for example potassium carbonate in methanol, and it may be carried out at ambient temperature or at an elevated temperature of up to 60° C.

The starting material of the formula II wherein A is a trans-vinylene radical, and Y is an oxygen or sulphur atom, used in the process of the invention may be obtained by reaction of the known aldehyde V (Ac = acetyl or *p*-phenylbenzoyl) with a phosphonate of the formula

$$(CH_3O)_2P^+O.^-CH.CO.X.Y.R^4$$

(which is prepared from dimethyl methylphosphonate and an ester of the formula

$$R^4.Y.X.COO \text{ alkyl},$$

in the presence of butyllithium), or with a phosphorane of the formula

$$Ph_3P:CH.CO.X.Y.R^4$$

(which is prepared from triphenylphosphine and a compound of the formula

$$R^4.Y.X.COCH_2I),$$

to give an unsaturated ketone VI. The ketone VI is reduced with zinc borohydride to the corresponding unsaturated alcohol VII, and the protecting acyl group is then removed with potassium carbonate in methanol to give a diol VIII. The diol VIII is protected as a bis-tetrahydropyranyl ether and the lactone ring is then reduced with di-isobutyl aluminium hydride to give a lactol X, or alternatively the diol VIII is reduced with disobutyl aluminium hydride to give a triol which may be acylated and selectively hydrolysed to give the lactol bis-ester (X, $R^5 = R^6 =$ acyloxy). The lactol X is reacted with the phosphonium ylide anion obtained from (4-carboxybutyl)-triphenylphosphonium bromide and a strong base, to give a carboxylic acid of the formula II.

The starting material of the formula II wherein A is an ethylene radical, and Y is an oxygen or sulphur atom, used in the process of the invention, may be obtained by hydrogenating an unsaturated ketone VI in the presence of 5% palladium-on-carbon catalyst, or with nickel boride, to give a saturated ketone XI, and repeating the procedure outlined above using the saturated ketone XI in place of the unsaturated ketone VI.

The starting material of the formula II wherein R^2 is an alkanoyloxy radical may be obtained from the corresponding compound wherein R^2 is a hydroxy radical by acylation with an acid anhydride in pyridine to give a 9-ester-1-mixed anhydride.

The starting material of the formula II, III or IV wherein R^2 and R^3 together form the oxo radical, may be obtained from the corresponding starting material of the formula II, wherein R^2 is hydroxy and R^3 is hydrogen, by oxidation with Jones' reagent (chromic acid in ketone), followed, as required, by hydroylsis of the tetrahydropyranyl protecting groups and esterification of the carboxylic acid group.

It is, of course, to be understood that an optically active compound of the invention may be obtained either by resolving the corresponding racemate, or by carrying out the above-described reaction sequences starting from an optically active intermediate, for example from an optically active aldehyde of the formula IV (Ac = acetyl or *p*-phenylbenzoyl).

composition of the invention is a sterile, substantially aqueous, injectable solution.

The compositions of the invention may be prepared by conventional means, and may incorporate conventional excipients.

The invention is illustrated, but not limited, by the following Examples:—

Example 1.

A solution of 9α - hydroxy - 16 - phenoxy-11α,15 - bis(tetrahydropyran - 2 - yloxy)-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoic acid (120 mg.) in 1.5 ml. of 2:1 mixture of acetic acid and water, was stirred at 50° C. for 4 hours. The solvents were evaporated, the residue was dissolved in dilute aqueous sodium bicarbonate solution (2 ml.) and the solution was extracted with ethyl acetate (3 × 2 ml.) and the extracts were discarded. The aqueous solution was acidified to pH 3—4 with 2N aqueous oxalic acid and the acidified solution was extracted with ethyl acetate (4 × 5 ml.). The ethyl acetate extracts where washed with a 1:1 mixture of saturated brine and water, and were then dried. After evaporation of the ethyl acetate, the residue consisted of a mixture of the C-15 epimers of 9α,11α,15 - trihydroxy - 16-phenoxy - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoic acid. Thin-layer chromatography on silica gel plates, supplied commercially by Merck of Darmstadt, using a mixture of benzene: dioxan: acetic acid (20:10:1) as the developing solvent, separated the C-15 epimers, having R_F values of 0.3 and 0.4, respectively. (Throughout this Example R_F values refer to silica gel plates supplied commercially by Merck of Darmstadt, and the spots were detected either by fluorescence, or by spraying the plates with a solution of ceric ammonium nitrate in sulphuric acid). The n.m.r. spectrum of each isomer (in deuterated acetone) showed the following characteristic bands (δ values):—

5.6—6.1, broad multiplet, 5 aromatic protons
4.2—4.8, broad multiplets, 4 olefinic protons
2.9—3.8, broad multiplets, 3H, *H*—C—O and 4 exchangeable protons

The bis-tetrahydropyranyl ether used as starting material may be prepared as follows:—

n-Butyl lithium (69 ml. of a 1.2M solution in hexane) was added to a solution of dimethyl methylphosphonate (10.3 g.) in dry tetrahydrofuran at −78° C. in an atmosphere of nitrogen. After 10 minutes, a solution of phenoxyacetyl chloride (4.1 g.) in dry tetrahydrofuran (20 ml.) was added dropwise, and the mixture was stirred for 4 hours at −78° C. The reaction mixture was neutralised with acetic acid and the solvents were removed under reduced pressure. The residue was shaken with a mixture of ether (100 ml.) and water (20 ml.), and the organic phase was separated and washed with brine. The solution was dried, the solvents were evaporated and the residue was distilled in a bulb distillation apparatus at an oven temperature of 160° C. and 0.1 mm. pressure, to give dimethyl 2 - oxo - 3 - phenoxypropylphosphonate.

A solution of dimethyl 2 - oxo - 3 - phenoxypropylphosphonate (1.01 g.) in dry 1,2-dimethoxyethane (20 ml.) at −78° C. was treated with n-butyl-lithium (2.75 ml. of a 1.2M solution in hexane), and the mixture was stirred for 15 minutes. To this mixture was added a solution of 4β - formyl - 2,3,3aβ,6aβ-tetrahydro - 2 - oxo - 5α - (p - phenylbenzoyloxy)cyclopenteno[b]furan (1.95 g.) in 1,2-dimethoxyethane (10 ml.), and after 1 hour the reaction mixture was neutralised with glacial acetic acid and all solvents were removed by evaporation under reduced pressure below 35° C. The residue was chromatographed on "Florisil" (trade mark) silica using solutions of ethyl acetate in methylene chloride as eluant, to yield the unsaturated ketone product as a white solid. [R_F = 0.6 (1:1 ethyl acetate/benzene)].

To a solution of the unsaturated ketone (500 mg.) in dry 1,2-dimethoxyethane (20 ml.) at 0° C. was added 1.5 ml. of a 0.5 M solution of zinc borohydride in 1,2-dimethoxyethane. The mixture was stired at room temperature for 30 minutes, then saturated sodium hydrogen tartrate solution was added until effervescence (10 ml.). 1N Hydrochloric acid (2.1 ml.) was added, the organic layer was separated, washed with a 1:1 mixture of saturated brine and water, then dried. The solvents were evaporated to give a mixture of epimeric unsaturated alcohols. [R_F = 0.3 (1:1 ethyl acetate/benzene)].

The mixture of epimeric unsaturated alcohols (500 mg.) was stirred vigorously for 2 hours with finely powdered anhydrous potassium carbonate (140 mg.) in methanol (10 ml.). 1N Hydrochloric acid (2.1 ml.) was added, followed by ethyl acetate (50 ml.). The organic layer was separated, washed successively with saturated sodium bicarbonate solution and saturated brine, and dried, and the solvents were evaporated. The residue was chromatographed on Florisil (20 g.). Elution with ether removed by-products, and subsequent elution with ethyl acetate gave a mixture of the C-15 epimeric diols [R_F = 0.2 (ethyl acetate)].

To a solution of the epimeric diols (316 mg.) in methylene chloride (3 ml.) under an atmosphere of nitrogen were added successively redistilled 2,3-dihydropyran (1.2 ml.) and a solution of anhydrous toluene-*p*-sulphonic acid in tetrahydrofuran (0.1 ml. of a 1% solution).

After 10 minutes, pyridine (3 drops) were added, followed by ethyl acetate (50 ml.). The solution was washed successively with

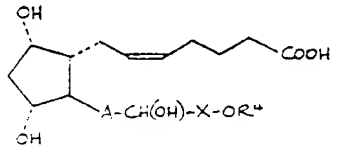
saturated sodium bicarbonate solution and saturated brine, and was dried. Evaporation of the solvents gave a mixture of epimeric bis-tetrahydropyranyl ethers as a clear oil. [R_F = 0.6 (ethyl acetate)].

To a solution of the epimeric bis-tetrahydropyranyl ethers (420 mg.) in dry toluene (10 ml.) under an atmosphere of nitrogen at −78° C. was added 1 ml. of a 2.2 mmole/ml. solution of di-isobutyl aluminium hydride in toluene. After 15 minutes the reaction was quenched by the dropwise addition of methanol (3 ml.) and after a further 15 minutes at room temperature a mixture of 1:1 saturated brine/water (25 ml.) was added, and the mixture was extracted with ethyl acetate (3 × 50 ml.). The extract was washed with saturated brine, and dried, and the solvents were evaporated to give a mixture of epimers of 2,3,3aβ,6aβ - tetrahydro - 2 - hydroxy - 4β - [4 - phenoxy-3 - (tetrahydropyran - 2 - yloxy) - 1 - *trans*-butenyl] - 5α - (tetrahydropyran - 2 - yloxy)-cyclopenteno[b]furan. [R_F = 0.4 (1:1 ethyl acetate/benzene)].

Finely powdered (4-carboxybutyl)triphenylphosphonium bromide (1.11 g.) was heated to 100° C. under vacuum for 1 hour. The evacuated reaction vessel was filled with an atmosphere of dry nitrogen, the solid was dissolved in dimethylsulphoxide (5 ml.) and the solution was cooled to room temperature. To this solution was added dropwise 2.35 ml. of a 2M solution of methanesulphinylmethyl sodium in dimethyl sulphoxide followed by a solution of the mixture of epimers of the cyclopenteno[b]furan bis-tetrahydropyranyl ether (400 mg.) in a mixture of dimethyl sulphoxide (10 ml.) and benzene (2 ml.). The solution was stirred for 3 hours, and the solvent was removed by evaporation under reduced pressure at a temperature below 40° C. The residue was shaken with water (10 ml.) and ethyl acetate (10 ml.) and the aqueous phase was separated, extracted with ethyl acetate (2 × 10 ml.) and the extracts discarded. The aqueous solution was acidified to pH 3—4 with 2N aqueous oxalic acid, and extracted with a mixture of equal parts of ether and petroleum ether (b.p. 40—60° C.) (5 × 10 ml.). The organic phase was separated, washed with saturated brine and was dried. Evaporation of the solvents gave 9α - hydroxy - 16 - phenoxy-11α,15 - bis(tetrahydropyran - 2 - yloxy)-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoic acid as a clear oil. [R_F = 0.5 (ethyl acetate)].

Example 2.

The process described in Example 1 was repeated, using the appropriate phosphonate reagent, to give the compounds shown below. The products were identified by n.m.r. spectroscopy and are characterised below either by R_F value on thin layer chromatography, or by accurate mass measurement by mass spectrometry of either the molecular ion or the (M^+ — methyl) ion, whichever is more appropriate, of the tetra (trimethylsilyl) derivative, which is prepared by adding to the compound to be mass measured bis-trimethylsilyl-trifluoroacetamide containing 1% trimethylchlorosilane (Regisil—trade mark) and leaving the mixture for 1 hour. In some cases, phosphonate reagent, or the unsaturated ketone intermediate in which Ac is *p*-phenylbenzoyl have been characterised and appropriate data for these compounds are also given.



No.	R_4	A	X
1	phenyl	—CH:CH—	—CH_2—
2	phenyl	—CH:CH—	—$CH(CH_3)$—
3	phenyl	—CH:CH—	—$C(CH_3)_2$—
4	phenyl	—CH:CH—	—$(CH_2)_3$—
5	benzyl	—CH:CH—	—CH_2—
6	2-naphthyl	—CH:CH—	—CH_2—
7	4-chlorophenyl	—CH:CH—	—CH_2—
8	4-chlorophenyl	—CH_2CH_2—	—CH_2—
9	3-chlorophenyl	—CH:CH—	—CH_2—
10	2-chlorophenyl	—CH:CH—	—CH_2—
11	2,4-dichlorophenyl	—CH:CH—	—CH_2—
12	4-bromophenyl	—CH:CH—	—CH_2—
13	4-fluorophenyl	—CH:CH—	—CH_2—
14	4-tolyl	—CH:CH—	—CH_2—
15	3-tolyl	—CH:CH—	—CH_2—
16	4-t-butylphenyl	—CH:CH—	—CH_2—
17	3-trifluoromethylphenyl	—CH:CH—	—CH_2—
18	4-methoxyphenyl	—CH:CH—	—CH_2—
19	2-methoxyphenyl	—CH:CH—	—CH_2—
20	4-biphenylyl	—CH:CH—	—CH_2—

No.	Isomer*	Mass spectrum		Phosphonate b.p. (°C./mm.)	Enone m.p. (°C.) (Formula VI)
		Found	Calculated		
1	mp lp	M^+=678.3610 M^+=678	678.3625	178—185/0.05	155—158
2	mp lp	M^+—CH_3=677.3540 M^+=692	677.3545 692	175/0.2	—
3	mixed	M^+—CH_3=691.3660	691.3702	130/0.1	—
4	mp lp	M^+=706.3921 M^+=706	706.3928	166—168/0.1	120—122
5	mixed	M^+=692.3753	692.3781	170/0.1	99—101
6	mp	M^+=728.3744	728.3781	m.p.=85—86°C.	185—187
7	mp lp	M^+—CH_3=697.2948 M^+=712	697.3001 712	170—173/0.1	132—135
8	mp(a) lp(a)	M^+=714.3399 M^+=714	714.3391	170—173/0.1	132—135
9	mp lp	M^+—CH_3=697.2297 M^+=712	697.3000 712	180/0.2	—
10	mp lp	M^+=712.3216 M^+712	712.3235	174—178/0.1	129—132
11	mp	M^+—CH_3=731.2599	731.2609	—	136—138
12	mixed	M^+—CH_3=741.2485	741.2497	—	—
13	mp lp	M^+=696.3468 M^+=696	696.3529	—	162
14	mixed	M^+=692.3738	692.3781	164/0.05	149
15	mp lp	M^+=692.3752 M^+=692	692.3781	180/0.5	140—141
16	mixed	M^+=734.4213	734.4251	—	—
17	mp lp	M^+=746.3467(b) (c)	746.3499		115—117
18	mp lp	M^+=708.3717 M^+=708	708.3731	—	—
19	mp lp	M^+=708.3710 M^+=708	708.3731	—	—
20	mp lp	M^+=754.3944 M^+=754	754.3938	m.p.=63—64°C.	—

* mp=more polar, lp=less polar isomer on silica gel thin layer chromatography.
(a) products synthesised from respectively the more polar and less polar enol intermediates.
(b) R_F=0.45 after 2 runs on silica gel t.l.c. with 5% acetic acid in ethyl acetate.
(c) R_F=0.50 after 2 runs on silica gel t.l.c. as for (b).

In the manufacture of compounds 8, wherein A is an ethylene radical, the unsaturated ketone intermediate is reduced to the saturated ketone as follows:—

The more polar epimer (epimers at C-3 of the butenyl side-chain) of 4β - (4 - *p* - chlorophenoxy - 3 - hydroxybut - 1 - *trans* - enyl)-2,3,3aβ,6aβ - tetrahydro - 2 - oxo - 5α-(*p* - phenylbenzoyloxy)cyclopenteno - [b]-furan (360 mg.) was dissolved in ethanol (25 ml.) and the solution was added to nickel boride, previously prepared from nickel acetate (620 mg.) and sodium borohydride (2.5 ml. of a 1 M solution). The mixture was shaken with hydrogen for 3 hours and was then filtered, and the filtrate was evaporated to dryness to give 4β - (4 - *p* - chlorophenoxy-3 - hydroxybutyl) - 2,3,3aβ,6aβ - tetrahydro-2 - oxo - 5α - (*p* - phenylbenzoyloxy)cyclopenteno[b] furan, R_F = 0.4 (50% ethyl acetate in toluene). The saturated ketone was then used, in place of the unsaturated ketone, in the remainder of the process described in Example 1.

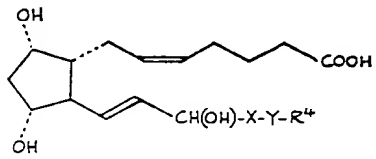
Example 3.

To a solution of the more polar C-15 epimer of 16 - (4 - chlorophenoxy) - 9α,11α,15-trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoic acid (15 mg.) in methanol (1 ml.) at 0° C. was added an excess of a solution of diazomethane in ether. After 10 minutes the solvents were evaporated to give a single C-15 epimer of methyl 16-(4 - chlorophenoxy) - 9α,11α,15 - trihydroxy-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoate as a clear oil, R_F = 0.3 (ethyl acetate). The n.m.r. spectrum showed the following characteristic bands (δ values):—

6.8—7.2, 4 aromatic protons
5.3—5.7, 4 olefinic protons
3.6, $COOCH_3$

Example 4.

The process described in Example 1 was repeated, using the appropriate phosphonate reagent, or an equivalent phosphorane $R^4—X—Y—CH_2.CO.CH:PPh_3$ to give the compounds shown below. The products were identified by n.m.r. spectroscopy and are characterised below either by R_F value on thin layer chromatography, or by accurate mass measurement by mass spectrometry of the molecular ion of the appropriate fully protected (trimethylsilyl) derivative, which is prepared by adding, to the compound to be mass measured, bis - trimethylsilyltrifluoroacetamide containing 1% trimethylchlorosilane (Regisil-trade mark) and leaving the mixture for 1 hour. In some cases, the phosphonate reagent, or the unsaturated ketone intermediate have been characterised and appropriate data for these compounds are also given.



No.	R^4	X	Y	Other substituents in prostanoic acid
21	phenyl	$-CH_2-$	$-N(CH_3)-$	—
22	4-chloropheny'	$-C(CH_3)_2-$	—O—	—
23	4-chlorophenyl	$-CH_2-$	—S—	—
24	3-fluorophenyl	$-CH_2-$	—O—	—
25	2-fluorophenyl	$-CH_2-$	—O—	—
26	3,4-dichlorophenyl	$-CH_2-$	—O—	—
27	2,5-dichlorophenyl	$-CH_2-$	—O—	—
28	2-tolyl	$-CH_2-$	—O—	—
29	2,3-xylyl	$-CH_2-$	—O—	—
30	3,5-xylyl	$-CH_2-$	—O—	—
31	2-chloro-4-methylphenyl	$-CH_2-$	—O—	—
32	3-dimethylaminophenyl	$-CH_2-$	—O—	—
33	1-naphthyl	$-CH_2-$	—O—	—
34	4-chloro-1-naphthyl	$-CH_2-$	—O—	—
35	2-naphthyl	$-CH_2-$	—O—	2-methyl
36	6-methyl-2-naphthyl	$-CH_2-$	—O—	—
37	6-methoxy-2-naphthyl	$-CH_2-$	—O—	—
38	3-chlorophenyl	$-CH_2-$	—O—	2-methyl
39	2,3-dichlorophenyl	$-CH_2-$	—O—	—
40	2,6-dichlorophenyl	$-CH_2-$	—O—	—
41	3,5-dichlorophenyl	$-CH_2-$	—O—	—
42	4-chloro-3-methylphenyl	$-CH_2-$	—O—	—
43	3-methoxyphenyl	$-CH_2-$	—O—	—
44	1-chloro-2-naphthyl	$-CH_2-$	—O—	—
45	5,6,7,8-tetrahydro-2-naphthyl	$-CH_2-$	—O—	—

No.	Isomer (a)	Mass spectrum Found	Mass spectrum Calculated	Phosphonate b.p. (°C./mm.)	Enone m.p. (°C.) (Formula VI)*
21	mp lp	M^+=691.3994 691	691.3940	(b)	145—150
22	mp lp	M—CH_3^+=725.3302	725.3313	150/0.05	(c)
23	mp lp	M^+=728.2977	728.3006	(b)	135—138
24	mp lp	M^+=696.3496 696	696.3531	(d)	138—139
25	mp lp	M^+=696.3510 696	696.3531	(e)	144
26	mp lp	M^+=746.2791 746	746.2844	(f)	150—152
27	mp lp	M^+=746.2799 746	746.2844	(g)	187—190
28	mp lp	M^+=692.3813 692	692.3781	154—160/0.05	165—167
29	mp lp	M^+=706.3971 706	706.3935	180/0.15	166—168
30	mp lp	M^+=706.3922 706	706.3935	—	140—142
31	mp lp	M^+=726 726	726	—	113—115
32	mp lp	M^+=721.4020 721	721.4047	(b)	138—145
33	mp lp	M^+=728.3830 728	728.3781	(h)	185—187
34	mp lp	M^+=762.3356 762	762.3388	(i)	(j)
35	mp lp	M^+742.3946 742	742.3937	m.p. 85—86	185—187
36	mp lp	M^+=742.3902 742	742.3937	m.p. 71—72	153
37	mp lp	M^+758.3910 758	758.3887	m.p. 58—59	195
38	mp lp	M^+=726.3346 726	726.3391	180/0.2	(k)
39	mp lp	M^+—CH_3=731.2644 M^+—CH_3=731	731.2609	175/0.03	153—155

No.
40
41
42
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44
45

(a) mp
(b) the
(c) R_F
(d) R_F
(e) R_F
(f) R_F
(g) R_F
(h) R_F
(i) R_F
(j) R_F
(k) R_F
(l) R_F
(m) R
(n) R_F
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No.	Isomer (a)	Mass spectrum Found	Mass spectrum Calculated	Phosphonate b.p. (°C./mm.)	Enone m.p. (°C.) (Formula VI)*
40	mp lp	M^+=746.2844 746	746.2844	m.p. 89—90	140—142
41	mp lp	M^+746.2829 746	746.2844	m.p. 80—82	138—139
42	mp lp	M^+=726.3397 726	726.3391	—	143
43	mp lp	M^+=708.3745 708	708.3730	(l)	129—130
44	mixed	M^+=762.3402	762.3391	m.p. 61—62	195
45	mp(m) lp(n)				

(a) mp=more polar, lp=less polar.
(b) these compounds synthesised from phosphoranes (not phosphonates), made as described below.
(c) R_F=0.5 (50% ethyl acetate in toluene).
(d) R_F=0.2 (40% ethyl acetate in methylene dichloride)
(e) R_F=0.4 (5% acetic acid in ethyl acetate)
(f) R_F=0.3 (50% ethyl acetate in chloroform)
(g) R_F=0.23 (50% ethyl acetate in chloroform)
(h) R_F=0.3 (50% ethyl acetate in methylene dichloride)
(i) R_F=0.4 (10% methanol in ethyl acetate)
(j) R_F=0.8 (50% ethyl acetate in toluene)
(k) R_F=0.6 (50% ethyl acetate in toluene)
(l) R_F=0.4 (50% ethyl acetate in methylene dichloride)
(m) R_F=0.25 (3% acetic acid in ethyl acetate)
(n) R_F=0.30 (3% acetic acid in ethyl acetate)
(m) and (n); δ 6.8 (1H, aromatic), 6.6 (2H, aromatic), 5.4 (2H, olefinic) and 5.7 (2H, olefinic).

* Ac is *p*-phenylbenzoyl.

The preparation of a phosphorane, which may be used in place of a phosphonate in the preparation of a cyclopentane derivative of the invention, is exemplified by the preparation of [3 - (3 - dimethylaminophenoxy)-acetonylidene] - triphenylphosphorane as follows: —

n-Butyl-lithium (3.85 ml. of a 1.3 M solution in hexane) was added to a solution of 3-dimethylaminophenol (685 mg.) in dimethoxyethane (20 ml.) at −70° C. under an atmosphere of nitrogen. The solution was allowed to warm to room temperature, a solution of 3 - iodoacetonylidene - triphenylphosphorane (2.22 g.) in benzene (100 ml.) was added, and the mixture was heated under reflux for 2 hours. The mixture was then diluted with toluene (100 ml.), washed with water (2 × 50 ml.) and dried, the solvents were evaporated and the residue was triturated with ether to give [3 - (3 - dimethylaminophenoxy) acetonylidene] triphenylphosphor - ane, m.p. 110—115° C.

In a similar manner were prepared the analogous N-methylanilino (gum) and 4-chlorophenylthio (m.p. 158—165° C.) phosphoranes.

Example 5.

The process described in Example 3 was repeated, using the appropriate more polar C-15 epimer, in place of the more polar C-15 epimer of 16 - (4 - chlorophenoxy)-9α,11α,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid, to give the following methyl esters as single C-15 epimers: —

a) methyl 16 - (4 - fluorophenoxy)-9α,11α,15 - trihydroxy - 17,18,19,20-tetranor - 5 - *cis* - 13 - *trans* - prostadienoate, R_F = 0.3 (5% methanol in toluene) δ = 6.8—7.2 (aromatic), 5.3—5.7 (4 olefinic protons), 3.6 (methyl ester).

b) methyl 9α,11α,15 - trihydroxy - 16-(2 - naphthyloxy) - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - prostadienoate, M^+ = 670.3542 (calculated 670.3541).

c) methyl 9α,11α,15 - trihydroxy - 2-methyl - 16 - (2 - naphthyloxy) - 17,18,19,20 - tetranor - 5 - *cis* - 13-*trans* - prostadienoate, M^+ = 684.3678 (calculated 684,3697).

d) methyl 9α,11α,15 - trihydroxy - 16-(6 - methyl - 2 - naphthyloxy) - 17,18,19,20 - tetranor - 5 - *cis* - 13-*trans* - prostadienoate, M^+ = 684.3739 (calculated 684.3698).

e) methyl 9α,11α,15 - trihydroxy - 16-(6 - methoxy - 2 - naphthyloxy)-17,18,19,20 - tetranor - 5 - *cis* - 13-*trans* - prostadienoate, M^+ = 700.3681 (calculated 700.3647).

f) methyl 16 - (3 - chlorophenoxy)-9α,11α,15 - trihydroxy - 17,18,19,20-tetranor - 5 - *cis* - 13 - *trans* - prostadienoate, R_F = 0.3 (ethyl acetate), M^+ = 654.2973 (calculated 654.2995).

g) methyl 9α,11α,15 - trihydroxy - 2-methyl - 16 - (3 - chlorophenoxy)-17,18,19,20 - tetranor - 5 - *cis* - 13-*trans* - prostadienoate, R_F = 0.4 (ethyl acetate), M^+ = 668.3133 (calculated 668.3151).

Example 6.

16 - (4 - Chlorophenoxy) - 9α,11α,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostanoic acid (20 mg. of the more polar C-15 epimer) was treated with an excess of dilute aqueous ammonia to form the ammonium salt. The excess of ammonia was evaporated under reduced pressure, and the residue was treated with the stoichiometric amount of silver nitrate to form the silver salt. The silver salt was filtered off, dried, dissolved in n-butyl iodide (0.5 ml.) and stirred at room temperature for 1 hour. The solution was extracted with ethyl acetate, the ethyl acetate extract was evaporated to dryness, and the residue was chromatographed on Florisil (1 g.) using 50% ethyl acetate in toluene as eluant, to give n-butyl 16-(4 - chlorophenoxy) - 9α,11α,15 - trihydroxy-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoate, M^+ for the tris-(trimethylsilyl) derivative = 696.3427 (calculated 696.3464), R_F = 0.4 (ethyl acetate).

In a similar manner, but using ethyl iodide in place of n-butyl iodide, there was obtained ethyl 16 - (4 - chlorophenoxy) - 9α,11α,15-trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoate, M^+ = 668.3086 (calculated 668.3151).

Example 7.

A solution of the mixed anhydride of acetic acid and the more polar C-15 epimer of 9α - acetoxy - 16 - (4 - chlorophenoxy)-11α,16 - bis(tetrahydropyran - 2 - yloxy)-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoic acid (73 mg.) in 2 ml. of a 2:1 mixture of acetic acid and water, was stirred at 47° C. under nitrogen for 4 hours. The solvents were evaporated, the residue was dissolved in dilute aqueous sodium bicarbonate solution (2 ml.) and the solution was extracted with ethyl acetate (3 × 2 ml.). The extracts were discarded, the aqueous solution was acidified to pH 3—4 with 2N aqueous oxalic acid and the acidified solution was extracted with ethyl acetate (4 × 5 ml.). The ethyl acetate extracts were washed with a 1:1 mixture of saturated brine and water, and were then dried. After evaporation of the ethyl acetate, the residue was purified by thin-layer chromatography on silica gel using 3% acetic acid in ethyl acetate, to give the more polar C-15 epimer of 9α - acetoxy - 16-(4 - chlorophenoxy) - 11α,15 - dihydroxy-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoic acid, M^+ = 682.2942 (calculated 682.2944).

The bis-tetrahydropyranyl ether used as starting material may be prepared as follows:—

A solution of the more polar C-15 epimer of 9α-hydroxy-16-(4-cholorphenoxy)-11α,15-bis(tetrahydropyran - 2 - yloxy) - 17,18,19,20-tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid (70 mg.) in 0.15 ml. of a 2:1 mixture of pyridine and acetic anhydride was kept at room temperature for 16 hours. The volatile material was evaporated and cyclohexane (10 ml.) was added to, and boiled off from, the residue three times, leaving the mixed anhydride of acetic acid and 9α - acetoxy - 16-(4 - chlorophenoxy) - 11α,15 - bistetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetranor-5 - *cis* - 13 - *trans* - prostadienoic acid as a yellow oil, ν max ($CHCl_3$) 1720, 1810 cm^{-1}.

Example 8.

To a solution of 9α - acetoxy - 16 - (4-chlorophenoxy) - 11α,15 - dihydroxy-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoic acid (12 mg.) in methanol (1 ml.) at 0° C. was added an excess of a solution of diazomethane in ether. After 10 minutes, the solvents were evaporated, the residue was dissolved in ether, and the solution was treated with lithium aluminium hydride (50 mg.). The mixture was stirred at room temperature for 1 hour, the excess of hydride was destroyed by the addition of water (1 ml.) and the mixture was extracted with ethyl acetate to give 16 - (4 - chlorophenoxy) - 9α,11α,15 - trihydroxy-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienol, M^+ = 698.3439 (calculated 698.3441), R_F = 0.2 (ethyl acetate).

In a similar manner, there were obtained:—

16 - (3 - chlorophenoxy) - 9α,11α,15 - trihydroxy - 2 - methyl - 17,18,19,20 - tetra-

nor - 5 - *cis* - 13 - *trans* - prostadienol, R_F = 0.15 (ethyl acetate, M^+ = 712.3575 (calculated 712.3597).

9α,11α,15 - trihydroxy - 16 - (6 - methyl-2 - naphthyloxy) - 17,18,19,20 - tetranor - 5-*cis* - 13 - *trans* - prostadienol, R_F = 0.2 (ethyl acetate).

Example 9.

The process described in Example 1 was repeated using the appropriate phosphonate reagent, to give:—

a) 9α,11α,15 - trihydroxy - 16 - (4-hydroxyphenoxy) - 17,18,19,20 - tetranor-5 - *cis* - 13 - *trans* - prostadienoic acid, R_F = 0.2 and 0.3 (3% acetic acid in ethyl acetate). δ = 6.82 (4H, aromatic), 5.3—5.7 (4H, olefinic), 3.98—5.1 (10H, >CH.O— and exchangeable protons); phosphonate, R_F = 0.2 (10% methanol in ethyl acetate); enone*, m.p. 135—140° C.

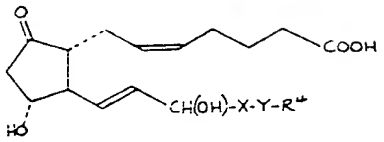
b) 16 - furfuryloxy - 9α,11α,15 - trihydroxy-17,18,19,20 - tetranor - 5 - *cis* - 13-*trans* - prostadienoic acid, R_F = 0.5 (3% acetic acid in ethyl acetate), δ = 7.5 (1H and 6.3 (2H) (furyl protons) 5.1—5.6 (4 H, olefinic); phosphonate, b.p. 200° C./0.2 mm; enone*, m.p. 92—93° C.

c) 16 - (3 - allylphenoxy) - 9α,11α,15-trihydroxy - 17,18,19,20 - tetranor - 5-*cis* - 13 - *trans* - prostadienoic acid, M^+ = 718.3892 (calculated 718.3938); phosphonate, R_F = 0.32 (ethyl acetate); enone*, m.p. 110—112° C.

* Formula VI. Ac is *p*-phenylbenzoyl.

Example 10

The process described in Example 1 was repeated, using a 9-oxo prostanoic acid derivative in place of a 9α-hydroxy prostanoic acid derivative, to give the compounds shown below. For measurement of mass spectra, the acids were converted to methyl esters with diazomethane, the 9-oxo group was protected by conversion to the methoxime with methoxylamine, and, where indicated, the hydroxy groups at C-11 and C-15 were protected as the trimethylsilyl derivatives. N.m.r. spectra were measured in deuterated acetone.



No.	R^4	X	Y
46	phenyl	$-CH_2-$	—O—
47	phenyl	$-CH(CH_3)-$	—O—
48	phenyl	$-(CH_2)_3-$	—O—
49	1-naphthyl	$-CH_2-$	—O—
50	2-naphthyl	$-CH_2-$	—O—
51	4-chlorophenyl	$-CH_2-$	—O—
52	4-chlorophenyl	$-CH_2-$	—S—
53	3-chlorophenyl	$-CH_2-$	—O—
54	2-chlorophenyl	$-CH_2-$	—O—
55	4-chlorophenyl	$-C(CH_3)_2$	—O—
56	4-bromophenyl	$-CH_2-$	—O—
57	4-fluorophenyl	$-CH_2-$	—O—
58	3-fluorophenyl	$-CH_2-$	—O—
59	2-fluorophenyl	$-CH_2-$	—O—
60	2,4-dichlorophenyl	$-CH_2-$	—O—
61	2,5-dichlorophenyl	$-CH_2-$	—O—
62	3,5-dichlorophenyl	$-CH_2-$	—O—
63	4-tolyl	$-CH_2-$	—O—
64	3-tolyl	$-CH_2-$	—O—
65	2-tolyl	$-CH_2-$	—O—
66	3,5-xylyl	$-CH_2-$	—O—
67	4-chloro-3-methyl-phenyl	$-CH_2-$	—O—
68	2-chloro-4-methyl-phenyl	$-CH_2-$	—O—
69	3-trifluoromethyl-phenyl	$-CH_2-$	—O—
70	4-methoxyphenyl	$-CH_2-$	—O—
71	2-methoxyphenyl	$-CH_2-$	—O—
72	4-chloro-1-naphthyl	$-CH_2-$	—O—

No.	Isomer*	Characterising Data
46	mixed	R_F=0.2 (acetone/cyclohexane/ethyl acetate—1:1:2) N.m.r.: δ 6.98—7.28 (5H, aromatic), 5.48 (2H, cis olefin), 5.78 (2H, trans olefin), 3.5—4.5 (5H, >CH.O— and —COOH)
47	mixed	M^+=589.3267 [calculated 589.3255 for methyl ester, 9-methoxime, 11,15-di-(trimethylsilyl) derivative]. R_F=0.4 (3% acetic acid in ethyl acetate)
48	mixed	R_F=0.3 (3% acetic acid in ethyl acetate)
49	mixed	R_F=0.4 (3% acetic acid in ethyl acetate). N.m.r.: aromatic protons oat δ 8.3—8.5 (1H), 7.7—7.9 (1H), 7.2—7.5 (4H) and 6.8—7.08 (1H)
50	mixed	R_F=0.3 (3% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ 7.7—7.8 (3H) and 7.1—7.5 (4H)
51	mp	M^+=609.2633 [calculated 609.2709 for methyl ester, 9-methoxime, 11,15-di (trimethylsilyl) derivative]. R_F=0.4 (3% acetic acid in ethyl acetate)
52	mixed	R_F=0.5 (3% acetic acid in ethyl acetate). N.m.r.:=aromatic protons at δ 7.3 (4H)
53	mp	R_F=0.3 (3% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ 7.15 (1H) and 6.9 (3H)
54	mixed	R_F=0.4 (3% acetic acid in ethyl acetate).
55	mixed	R_F=0.5 (3% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ 7.28 (2H), 7.19 (2H) and 2 methyls at δ 1.25 and 1.30 (6H)
56	mixed	M^+=509.1417 (calculated 509.1413 for methyl ester, 9-methoxime)
57	mixed	R_F=0.3 (3% acetic acid in ethyl acetate) N.m.r.: aromatic protons at δ 6.91 (2H) and 7.08 (2H)
58	mixed	R_F=0.3 (2% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ 7.25 (1H) and 6.65 (3H)

No.	Isomer*	Characterising Data
59	mixed	R_F=0.4 (5% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ 7.05 (4H)
60	mixed	R_F=0.4 (0.25% acetic acid in ethyl acetate) N.m.r.: aromatic protons at δ 7.12 (1H), 7.3 (1H) and 7.41 (1H)
61	mixed	R_F=0.34 (3% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ 7.3 (1H), 7.15 (1H) and 6.9 (1H)
62	mixed	R_F=0.34 (3% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ 6.9 (3H)
63	mixed	R_F=0.2 (cyclohexane/ethyl acetate/acetone, 2:2:1). N.m.r.: aromatic protons at δ 6.7 (2H) and 7.1 (2H), and methyl at δ 2.28
64	mixed	R_F=0.5 (3% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ7.05 (1H) and 6.73 (3H), and methyl at δ 2.28
65	mixed	M^+=589.3284 [calculated 589.3254 for methyl ester, methoxime, di (trimethylsilyl) derivative]. R_F=0.35 (3% acetic acid in ethyl acetate)
66	mixed	R_F=0.2 (cyclohexane/acetone/ethyl acetate—4:1:2). N.m.r.: aromatic protons at δ 6.5 (3H), and methyls (6H) at 2.28
67	mixed	R_F=0.5 (5% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ 7.2 (1H) and 6.85 (2H), and methyl at 2.3
68	mixed	R_F=0.4 (cyclohexane/ethyl acetate/acetone—4:2:1). N.m.r.: aromatic protons at δ 7.18 (1H) and 6.80 (2H), and methyl at 2.2
69	mp	R_F=0.5 (5% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ 7.5 (1H) and 7.25 (3H)
70	mixed	R_F=0.6 (3% acetic acid in ethyl acetate)
71	mixed	R_F=0.65 and 0.7 (3% acetic acid in ethyl acetate)
72	mixed	R_F=0.4 (3% acetic acid in ethyl acetate). N.m.r.: aromatic protons at δ 8.4 (1H), 8.15 (1H), 7.6 (3H) and 7.08 (1H)

* mp=more polar.

The 9-oxo prostanoic acid derivatives used as starting materials may be obtained by oxidation of the corresponding 9α-hydroxy compound, as exemplified below for the preparation of 9 - oxo - 16 - phenoxy - 11α,15-bis(tetrahydropyran - 2 - yloxy) - 17,18,19,20-tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid:—

To a solution of 9α - hydroxy - 16 - phenoxy - 11α,15 - bis(tetrahydropyran - 2-yloxy) - 17,18,19,20 - tetranor - 5 - *cis* - 13-*trans* - prostadienoic acid (270 mg.) in acetone (5 ml.) at −10° C. was added Jones' reagent (chromic acid in acetone), 0.163 ml.). After 15 minutes, isopropanol (1 drop) was added, followed by ethyl acetate (20 ml). The solution was washed with 1:1 saturated brine/water, and was dried. Evaporation of the solvents, and chromatography of the residue on silica, using 1:1 ether/petroleum ether (b.p. 40—60° C.) as eluting solvent, gave the required 9-oxo-bis(tetrahydropyranyl ether), R_F = 0.2 (50% ethyl acetate in toluene).

Example 11.

The process described in Example 3 was repeated, using 11α,15 - dihydroxy - 16 - (2-naphthyloxy) - 9 - oxo - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid, in place of 16 - (4 - chlorophenoxy)-9α,11α,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid, to give methyl 11α,15 - dihydroxy - 16 - (2-naphthyloxy) - 9 - oxo - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - prostadienoate, R_F = 0.3 (ethyl acetate).

Example 12.

To a solution of 16 - (4 - chlorophenylthio) - 9α,11α,15 - trihydroxy - 17,18,19,20-tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid (12 mg.) in methanol (0.5 ml.) at 0° C. was added a solution of sodium periodate (5 mg.) in water (0.5 ml.). After 18 hours the solvents were evaporated, and the residue was extracted with acetone to give 16 - (4-chlorophenylsulphinyl) - 9α,11α,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoic acid, M^+ = 744.2918 (calculated 744.2956), R_F = 0.2 (3% acetic acid in ethyl acetate).

Example 13.

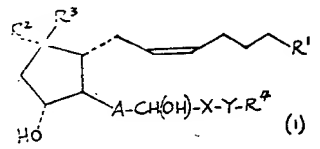
	% w/v
16 - (4 - fluorophenoxy) - 9α,11α,15-trihydroxy - 17,18,19,20 - tetranor-5 - *cis* - 13 - *trans* - prostadienoic acid	0.003
Sodium phosphate	2.90
Sodium hydrogen phosphate	0.30
Water for injection	to 100

The sodium phosphate was dissolved in about 80% of the water, followed by the prostadienoic acid derivative, and, when dissolved, the sodium hydrogen phosphate. The solution was made up to volume with water for injection, and the pH was checked to be between 6.7 and 7.7. The solution was filtered to remove particulate matter, sterilised by filtration, and filled into presterilised neutral glass ampoules under aseptic conditions. Immediately before use, the contents of an ampoule are diluted in sodium chloride B.P. for administration by intravenous infusion.

The prostadienoic acid derivative may, of course, be replaced by an equivalent amount of another prostanoic acid derivative of the invention.

WHAT WE CLAIM IS:—

1. A prostanoic acid derivative of the formula:—



(I)

wherein R^1 is a hydroxymethyl or carboxy radical, or an alkoxycarbonyl radical of up to 11 carbon atoms; either R^2 is a hydroxy radical or an alkanoyloxy radical of 1 to 4 carbon atoms and R^3 is a hydrogen atom, or R^2 and R^3 together form the oxo radical; A is an ethylene or trans-vinylene radical; X is an alkylene radical of 1 to 3 carbon atoms bearing as substituents 0, 1 or 2 alkyl radicals, each of 1 to 3 carbon atoms; Y is an oxygen or sulphur atom, a sulphinyl (—SO—) radical or an alkylimino (—NAlkyl—) radical of up to 4 carbon atoms; and R^4 is an aryl, benzyl or furfuryl radical which is unsubstituted or which is substituted by halogen atoms, hydroxy, nitro or phenyl radicals, alkyl, alkenyl, halogenoalkyl, alkoxy, alkenyloxy or acylamino radicals of up to 4 carbon atoms or dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms; which compound contains 0 or 1 alkyl radical of up to 4 carbon atoms on carbon atom 2, 3 or 4; and for those compounds wherein R^1 is a carboxy radical, the pharmaceutically acceptable salts thereof.

2. A prostanoic acid derivative as claimed in claim 1 wherein R^1 is a hydroxymethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, n-butoxycarbonyl or n-decyloxycarbonyl radical; R^2 is a hydroxy, acetoxy or propionyloxy radical and R^3 is a hydrogen atom, or R^2 and R^3 together form the oxo radical; A has the meaning defined in claim 1; X is a methylene, ethylene or trimethylene radical bearing 0, 1 or 2 methyl substituents; Y is an oxygen or sulphur atom, or the sulphinyl or methylimino radical; and R^4 is a phenyl, naphthyl, benzyl or furfuryl radical containing as substituents not more than two halogen

atoms, phenyl, hydroxy, methyl, t-butyl, allyl, methoxy or allyloxy radicals, chloroalkyl or fluoroalkyl radicals each of 1 to 4 carbon atoms or dimethylamino radicals; which compound contains 0 or 1 alkyl radicals of up to 4 carbon atoms on carbon atom 2, 3 or 4; and for those compounds wherein R^1 is a carboxy radical the ammonium, alkylammonium containing 1 to 4 alkyl radicals each of 1 to 6 carbon atoms, alkanolammonium containing 1 to 3 2-hydroxyethyl radicals, and alkali metal salts thereof.

3. A prostanoic acid derivative of the formula I shown in claim 1, wherein R^1 is a hydroxymethyl, carboxy, methoxycarbonyl, ethoxycarbonyl or n-butoxycarbonyl radical; R^2 is a hydroxy or acetoxy radical and R^3 is a hydrogen atom, or R^2 and R^3 together form the oxo radical; A is the ethylene or trans-vinylene radical; X is the methylene, ethylidene, isopropylidene or trimethylene radical; Y is an oxygen or sulphur atom, or the sulphinyl or methylimino radical; and R^4 is the furfuryl or benzyl radical, or a phenyl or naphthyl radical containing as substituents not more than two chlorine, bromine or fluorine atoms, or phenyl, hydroxy, methyl, t-butyl, allyl, methoxy, trifluoromethyl or dimethylamino radicals; which compound optionally bears a methyl substituent on carbon atom 2.

4. A prostanoic acid derivative as claimed in any preceding claim wherein R^4 is a chlorophenyl, chloronaphthyl, bromophenyl, fluorophenyl, tolyl, xylyl, methylnaphthyl, t-butylphenyl, methylchlorophenyl, trifluoromethylphenyl, hydroxyphenyl, methoxyphenyl, methoxynaphthyl, biphenylyl, dimethylaminophenyl or tetrahydronaphthyl radical.

5. A prostanoic acid derivative as claimed in any preceding claim wherein R^4 is the phenyl, benzyl, furfuryl, 1-naphthyl, 2-naphthyl, 2-, 3- or 4-chlorophenyl, 4-bromophenyl, 2-, 3- or 4- fluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2-, 3- or 4-tolyl, 2,3-, 3,4- or 3,5-xylyl, 4-t-butylphenyl, 3-allylphenyl, 3-trifluoromethylphenyl, 4-hydroxyphenyl, 2-, 3- or 4-methoxyphenyl, 4-biphenylyl, 3-dimethylaminophenyl, 2-chloro-4-methylphenyl, 4-chloro-3-methylphenyl, 1-chloro-2-naphthyl, 4-chloro-2-naphthyl, 6-methyl-2-naphthyl, 6-methoxy-2-naphthyl or 5,6,7,8-tetrahydro-2-naphthyl radical.

6. A prostanoic acid derivative of the formula I shown in claim 1, wherein R^1 is a carboxy radical or an alkoxycarbonyl radical of up to 6 carbon atoms; either R^2 is a hydroxy radical or an alkanoyloxy radical of 1 to 4 carbon atoms and R^3 is a hydrogen atom, or R^2 and R^3 together form the oxo radical; A is an ethylene or *trans*-vinylene radical; X is an alkylene radical of 1 to 3 carbon atoms bearing as substituents 0, 1 or 2 alkyl radicals, each of 1 to 3 carbon atoms; and R^4 is an aryl radical, which is unsubstituted or which is substituted by halogen atoms, nitro radicals, alkyl, alkoxy or acylamino radicals of 1 to 4 carbon atoms or dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms; and for those compounds wherein R^1 is a carboxy radical, pharmaceutically acceptable salts thereof.

7. A prostanoic acid derivative of the formula I given in claim 1 wherein R^1 is a hydroxymethyl or carboxy radical, or an alkoxycarbonyl radical of up to 7 carbon atoms; either R^2 is a hydroxy radical or an alkanoyloxy radical of 1 to 4 carbon atoms and R^3 is a hydrogen atom, or R^2 and R^3 together form the oxo radical; A is an ethylene or *trans*-vinylene radical; X is an alkylene radical of 1 to 3 carbon atoms bearing as substituents 0, 1 or 2 alkyl radicals, each of 1 to 3 carbon atoms; and R_4 is an aryl or benzyl radical, which is unsubstituted or which is substituted by halogen atoms, nitro or phenyl radicals, alkyl, halogenoalkyl, alkoxy or acylamino radicals of 1 to 4 carbon atoms or dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms; and those compounds wherein R^1 is a carboxy radical, pharmaceutically acceptable salts thereof.

8. A prostanoic acid derivative as claimed in any one of claims 1, 2, 3, 6 and 7 wherein R^4 is a chlorophenyl, fluorophenyl, trifluoromethyl or unsubstituted naphthyl radical.

9. A prostanoic acid derivative as claimed in any one of claims 1, 2, 3, 6 and 7 wherein R^1 is a carboxy or methoxycarbonyl radical and R^4 is a chlorophenyl, fluorophenyl, trifluoromethyl or unsubstituted naphthyl radical.

10. A prostanoic acid derivative as claimed in any one of claims 1, 2, 3 and 7 wherein R^1 is the hydroxymethyl radical and R^4 is a chlorophenyl, fluorophenyl, trifluoromethyl or unsubstituted naphthyl radical.

11. A prostanoic acid derivative as claimed in any one of claims 8, 9 and 10 wherein R^4 is the 3- or 4-chlorophenyl, 2- or 4-fluorophenyl, 3-trifluoromethylphenyl or 2-naphthyl radical.

12. A prostanoic acid derivative of the formula I given in claim 1, wherein R^1 is the carboxy or methoxycarbonyl radical, R^2 is the hydroxy radical and R^3 is a hydrogen atom or R^2 and R^3 together form the oxo radical, A is the *trans*-vinylene radical, X is the methylene or isopropylidene radical, Y is an oxygen atom and R^4 is the 3- or 4-chlorophenyl, 2- or 4-fluorophenyl, or 2-naphthyl radical.

13. A prostanoic acid derivative of the formula I given in claim 1 wherein R^1 is the carboxy, methoxycarbonyl or hydroxymethyl radical, R^2 is a hydroxy radical and R^3 is a hydrogen atom, or R^2 and R^3 together form the oxo radical, A is the *trans*-vinylene radical, X is the methylene or isopropylidene radical, Y is an oxygen atom and R^4 is the 3-

or 4-chlorophenyl, 2- or 4-fluorophenyl, 3-trifluoromethylphenyl or 2-naphthyl radical.

14. A prostanoic acid derivative as claimed in claim 12 or 13 which additionally bears a methyl substituent on carbon atom 2.

15. The compounds 16 - (4 - fluorophenoxy) - 9α,11α,15 - trihydroxy - 17,18,19,20-tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid, methyl 16 - (4 - fluorophenoxy)-9α,11α,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - prostadienoate, 16 - (2 - fluorophenoxy) - 9α,11α,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoic acid, 16 - (4-chlorophenoxy) - 9α,11α,15 - trihydroxy-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoic acid, methyl 16 - (4 - chlorophenoxy) - 9α,11α,15 - trihydroxy-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoate, 16 - (3 - chlorophenoxy)-9α,11α,15 - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans* - prostadienoic acid, methyl 16 - (3 - chlorophenoxy) - 9α,11α,15-trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoate, 9α,11α,15-trihydroxy - 16 - (2 - naphthyloxy)-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoic acid, and 16 - (4 - chlorophenoxy) - 9α,11α,15 - trihydroxy - 16,16-dimethyl - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienoic acid.

16. The compounds 16 - (4 - chlorophenoxy) - 9α,11α,15 - trihydroxy - 17,18,19,20-tetranor - 5 - *cis* - 13 - *trans* - prostadienol and 9α,11α,15 - trihydroxy - 16 - (3 - trifluoromethylphenoxy) - 17,18,19,20 - tetranor-5 - *cis* - 13 - *trans* - prostadienoic acid.

17. The compound 16 - (3 - chlorophenoxy) - 9α,11α,15 - trihydroxy - 2-methyl - 17,18,19,20 - tetranor - 5 - *cis*-13 - *trans* - prostadienol.

18. The compound 16 - (4 - chlorophenoxy) - 11α,15 - dihydroxy - 9 - oxo-17,18,19,20 - tetranor - 5 - *cis* - 13 - *trans*-prostadienoic acid.

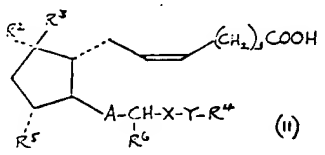
19. A compound as claimed in any preceding claim which is the more polar of the C-15 epimers as shown by thin layer chromatography.

20. A compound as claimed in any preceding claim which is in a racemic form.

21. A compound as claimed in any one of claims 1 to 19 which is in a luteolytically effective, optically-active form.

22. A process for the manufacture of a prostanoic acid derivative as claimed in claim 1 which comprises: —

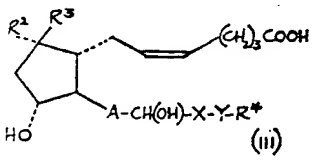
(a) for those compounds wherein R^1 is a carboxy radical, the hydrolysis of a compound of the formula: —



(II)

or of a mixed anhydride thereof, wherein A, X, Y, R^2, R^3 and R^4 have the meanings stated above, and R^5 and R^6 are each a tetrahydropyran-2-yloxy radical, or an acyloxy radical of 1 to 6 carbon atoms, whereafter when a salt is required the product is reacted with a base; or

(b) for those compounds wherein R^1 is an alkoxycarbonyl radical of up to 11 carbon atoms, the reaction of an acid of the formula: —



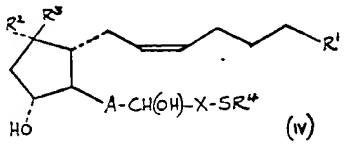
(III)

wherein A, X, Y, R^2, R^3 and R^4 have the meanings stated above, with a diazoalkane of the formula $R^7.N_2$, wherein R^7 is an alkyl radical of 1 to 10 carbon atoms; or

(c) for those compounds wherein R^1 is an alkoxycarbonyl radical of up to 11 carbon atoms, the reaction of a salt of an acid of the formula II with an alkyl halide of 1 to 10 carbon atoms; or

(d) for those compounds wherein R^1 is the hydroxymethyl radical and Y is an oxygen or sulphur atom or an alkylimino radical, the reduction of an ester of the formula I wherein R^1 is an alkoxycarbonyl radical of up to 11 carbon atoms; or

(e) for those compounds wherein Y is the sulphinyl radical, the oxidation of a thiocompound of the formula: —



(IV)

wherein R^1, R^2, R^3, R^4, A and X have the meanings defined in claim 1.

23. A process as claimed in claim 22 wherein the hydrolysis is carried out in an aqueous or alcoholic solution of an alkali metal carbonate.

24. A process as claimed in claim 22 which

is carried out with a solution of potassium carbonate in methanol.

25. A process as claimed in claim 22 wherein the salt of an acid of the formula II is the silver salt.

26. A process as claimed in claim 22 wherein the alkyl halide is an alkyl iodide.

27. A process as claimed in claim 22 wherein the reduction is carried out with a complex metal hydride.

28. A process as claimed in claim 27 wherein the complex metal hydride is lithium aluminium hydride.

29. A process as claimed in claim 22 wherein the oxidation is carried out with sodium periodate.

30. A pharmaceutical or veterinary composition which comprises a prostanoic acid derivative as claimed in claim 1 together with a pharmaceutically or veterinarily acceptable diluent or carrier.

31. A composition as claimed in claim 30 which is in a form suitable for oral administration, for inhalation, for parenteral administration, or for anal or vaginal use.

32. A composition as claimed in claim 31 which is a tablet, capsule, aerosol, solution suitable for spraying, sterile injectable aqueous or oily solution or suspension, or a suppository.

33. A composition as claimed in claim 30 which is a sterile, substantially aqueous solution containing from 0.01 to 10 μg./ml. of the prostanoic acid derivative.

34. A prostanoic acid derivative as claimed in claim 1 substantially as hereinbefore described in any one of Examples 1 to 12.

35. A prostanoic acid derivative as claimed in claim 6 substantially as hereinbefore described in Example 1.

36. A prostanoic acid derivative as claimed in claim 7 substantially as hereinbefore described in any one of Examples 1 to 3.

37. A pharmaceutical or veterinary composition as claimed in claim 30 substantially as hereinbefore described in Example 13.

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